Influence of Cosolvents and Surfactants on the Rate Constant (Log K) of Sparfloxacin

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Abstract

Sparfloxacin, a difluoroquinolone antibacterial agent is clinically used in the treatment of streptococci and community-acquired lower respiratory tract infections. The aim of the present study was to investigate to what extent cosolvents and surfactants could affect sparfloxacin degradation kinetics under acidic condition. The degradation of sparfloxacin in acidic aqueous solution of cosolvents and surfactants at $60 \pm 0.2°C$ was studied. The degradation was determined by UV spectrometry. The degradation was observed to follow apparent first-order rate kinetics and the rate constants for the decomposition were obtained from plots of logarithm percent drug concentration remaining versus time. The reaction was shown to be hydrogen ion catalysed. Significant increase in the stability of sparfloxacin was observed with the cosolvents and surfactants investigated. The study suggests that cosolvents or surfactants at non-toxic concentrations could be incorporated into liquid pharmaceutical dosage forms of sparfloxacin to stabilize the preparations under acidic conditions.

Keywords: Sparfloxacin; Degradation kinetics; Cosolvents; Surfactants; Rate constant
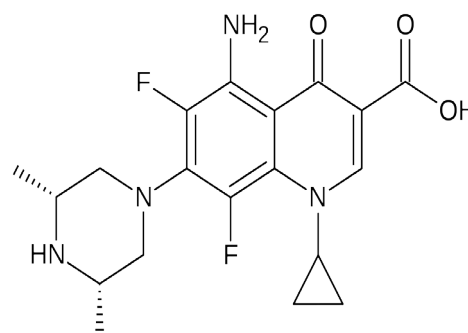
Introduction

Sparfloxacin **(Figure 1)**, chemically defined as 5-amino-1-cyclopropyl-7-(cis-3, 5-dimethyl-1- piperazinyl)-6, 8-difluoro-1, 4-dihydro-4-oxo-3-quinolinecarboxylic acid is a difluoroquinolone antibacterial agent belonging to the third generation quinolones. It is insoluble in water [1]. In clinical practice, sparfloxacin is used to treat streptococci and community-acquired lower respiratory tract infections [2-5] **Figure 1**. Its mechanism of action involves inhibition of DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase and type IV topoisomerase, therefore resulting in rapid bacterial death [6]. Sparfloxacin is water-insoluble and belongs to class II of the Bio pharmaceutics classification System. Cosolvents are organic compounds found to be substantially miscible with water [7]. They have been reported to have significant effects on the rate constants of chemical compounds. [8,9]. Surfactants are amphiphilic molecules composing of a hydrophilic polar moiety (head) and a hydrophobic non-polar moiety (tail) and capable of forming colloidal-sized clusters in solutions, called micelles [10]. Surfactants have also been reported to have great influence on the rate constants of chemical compounds [11]. Previous study [12] has shown that sparfloxacin undergoes degradation under acidic conditions. Literature search has revealed that no study has been done to investigate the influence of cosolvents and surfactants on sparfloxacin degradation. Therefore, this study was aimed at determining the influence of cosolvents and surfactants on the rate constant of sparfloxacin by investigating its degradation kinetics in acidic aqueous solution.

Materials and Methods

Materials

Sparfloxacin (Baroque Pharmaceuticals PVT. Ltd, India), glycerol,

Figure 1 Chemical structure of sparfloxacin.

propylene glycol, polyethylene glycol 400, sodium lauryl sulphate and polysorbate 80 (tween 80). All were purchased from Sigma-Aldrich, USA. Methanol, hydrochloric acid and sodium hydroxide (Fisher Scientific, USA. UV/Vis Spectrophotometer (Shimadzu, Japan).

Sample preparation

Standard stock solution of 200 µg/ml of sparfloxacin was prepared by dissolving accurately weighed 10 mg of sparfloxacin in 50 ml of methanol. The stock solution was used to obtain the wavelength of maximum absorption of the drug by scanning with a UV/V is Spectrophotometer. Dilution of the stock solution was done to obtain concentrations of 1, 2, 3, 4 and 5 µg/ml respectively. The absorbance readings of these concentrations were taken at wavelength of 304 nm to obtain the calibration graph of sparfloxacin.

Vehicle preparation

A 0.1 M HCl solution was prepared by diluting 8.3 ml of concentrated HCl in distilled water and diluted to 1000 ml with distilled water, while 0.1 M NaOH was prepared by dissolving 4 gms of NaOH pellets in distilled water and making the final volume up to 100 ml with distilled water. A stock solution of 25% w/v of the three cosolvents used were prepared by weighing 25 gms of each cosolvent into a beaker, dissolving in distilled water, and the volume made up to 100 ml in a volumetric flask with distilled water. Dilution of the stock solution was made in 0.1 M HCl solution to obtain concentrations of 20% w/v, 15% w/v, 10% w/v, 5% w/v respectively. Similarly, a stock solution of 2.0% w/v of the two surfactants used were prepared by weighing 2 gms of each surfactant into a beaker and dissolving in distilled water, and the volume made up to 100 ml in a volumetric flask with distilled water. Dilution of the stock solution was made in 0.1 M HCl solution to obtain concentrations of 1.0% w/v, 0.5% w/v, 0.2% w/v, 0.1% w/v respectively.
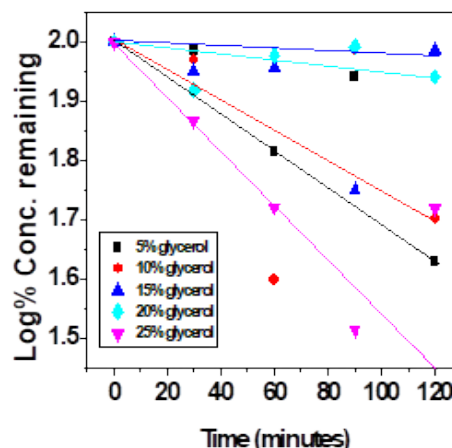
Kinetic study

The kinetic study was done by introducing 1 ml of the drug stock solution (200 µg/ml) into a 10 ml volumetric flask, diluted to volume with various percentage solutions of the cosolvent and surfactant respectively. The solutions were transferred into vials, capped and placed into a water bath at a temperature of 600°C. At intervals of 30 mins, samples were withdrawn from the water bath and analysed spectrophotometrically at a maximum wavelength of 304 nm. A plot of log percent remaining of the drug versus time was carried out to obtain the rate constant.
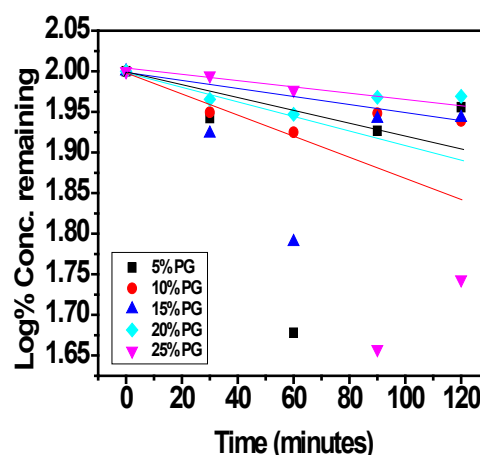
Results

The calibration graph of sparfloxacin obtained by plotting absorbance *versus* concentration gave a linear curve. Beer's law was obeyed in the concentration range of 1-5 µg/ml. The regression equation for the linear graph is A=0.0505C+0.002. The results of the kinetic studies of sparfloxacin in cosolvent acidic solutions are presented in **Figures 2-4** while that of surfactant solutions are given in **Figures 5 and 6**. The results showed that the plot of logarithm of percent sparfloxacin remaining versus time gave linear curves for all the vehicles investigated. The
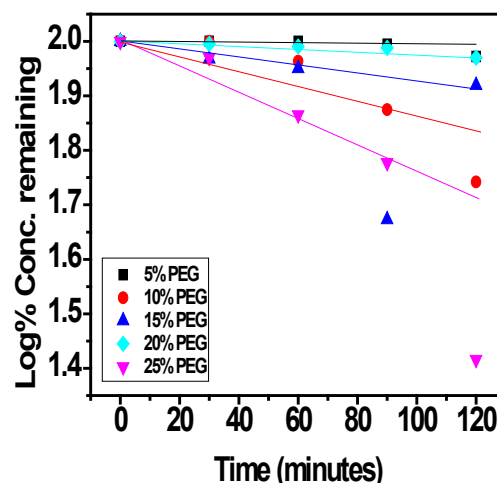
effects of the cosolvents and surfactants on the rate constant are presented in **Tables 1 and 2** respectively. The results showed that all the vehicles studied decreased the rate constant.

Figure 2 Effect of glycerol on the degradation kinetics of sparfloxacin.

Figure 3 Effect of propylene glycol on the degradation kinetics of sparfloxacin.

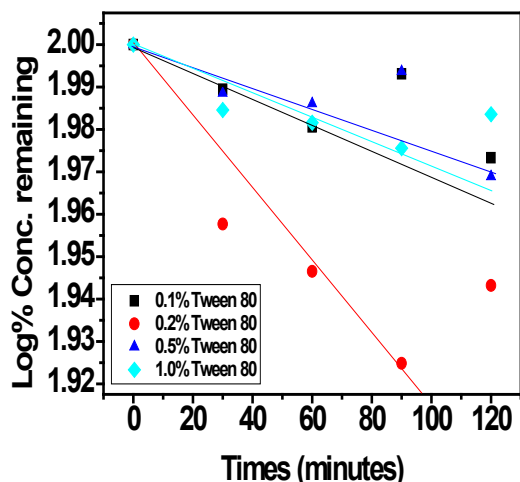**Figure 4** Effect of polyethylene glycol400 on the degradation kinetics of sparfloxacin.

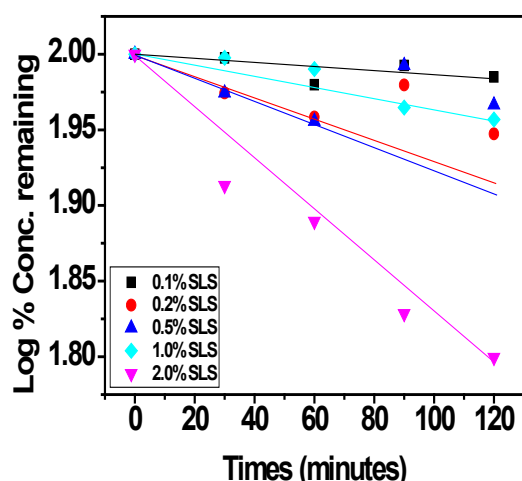**Figure 5** Effect of tween 80 on the degradation kinetics of sparfloxacin.

Figure 6 Effect of sodium lauryl sulphate on the degradation kinetics of sparfloxacin.

Table 1 Effect of cosolvents on the rate constant of sparfloxacin.

	Rate constant (k)		
% Cosolvent	Glycerol	Propylene glycol	Polyethylene glycol
5	0.00702	0.00652	0.01043
10	0.00603	0.00095	0.00493
15	0.00603	0.0008	0.0035
20	0.00176	0.00074	0.00052
25	0.00033	0.00045	0.00047

Table 2 Effect of surfactant on the rate constant of sparfloxacin.

	Rate constant (k)	
% w/v Surfactant	Polysorbate 80	Sodium lauryl sulphate
0.1	0.00251	0.00373
0.2	0.00114	0.00091
0.5	0.00044	0.00077
1	0.00038	0.00036
2	0.00032	0.00027

Discussion

Chemical stability of pharmaceutical active agents is a matter of great concern as it affects efficacy and safety of the drug product. Cosolvents and surfactants are among the techniques used to stabilize drug degradations. The linearity of the calibration curve was confirmed by regression correlation coefficient (R^2) value of 0.9881. In the kinetic study, a plot of logarithm of percent drug remaining versus time gave a linear graph for each vehicle studied. The slopes of the linear graphs allowed the rate constants to be evaluated. The rate constant obtained in 0.1 M HCl solution was used as a control in evaluating the effect of the studied vehicles on the rate constant of sparfloxacin. Previous studies have used plots of logarithm of percent drug remaining versus time to calculate kinetic rate constants of drugs [9,13]. A general hypothetical rate equation for sparfloxacin degradation as a function of 0.1 M HCl can be written as, $k_{obs}=k_o+k[H+]$, where k_{obs} is the overall observed rate constant, k_o is the water catalysis rate constant, $k[H+]$ is the hydrogen ion catalysis rate constant. The water catalysis rate constant is an apparent first-order rate constant while the hydrogen ion catalysis rate constant is second-order rate constant. The degradation of sparfloxacin in these vehicles (cosolvent and surfactant solutions) followed first-order rate kinetics. The rate constant decreased as the content of each vehicle was increased. It was also observed that glycerol showed most decreasing effect on the rate constant of sparfloxacin than the other cosolvent systems at the maximum concentration (20.0% w/v) studied. The stabilization effect of the cosolvent on sparfloxacin degradation may perhaps be due to decrease in dielectric constant and changes in viscosity of the solutions. A plot of logarithm of the rate constant versus cosolvent concentration showed a linear relationship. Similarly, it was noted that sodium lauryl sulphate showed slightly more decreasing effect on the rate constant of sparfloxacin than polysorbate 80 (tween 80) at the maximum concentration (2.0% w/v) investigated. A linear relationship was also observed when logarithm of the rate constant versus cosolvent concentration was plotted. The effect of surfactants on the rate constants might be due to micelle formation or a combination of micelle formation and pH effects. In this investigation, no attempt was made to carry out effects of buffers, ionic strength, pH, temperature on the sparfloxacin degradation or characterize the degradation products because information on them has been reported [12]. However, a plausible reaction mechanism of the hydrolysis is the decarboxylation of the drug molecule.

Conclusion

The breakdown of sparfloxacin was found to be first-order rate kinetics and the hydrolytic reaction was hydrogen ion catalysed. Glycerol exhibited greatest stabilizing properties on the rate constant of sparfloxacin than propylene glycol and polyethylene glycol 400 respectively. Similarly, sodium lauryl sulphate showed greater stabilizing effect on the rate constant of sparfloxacin than polysorbate 80. Finally, the study suggests that the incorporation of cosolvents or surfactants investigated into liquid pharmaceutical dosage forms containing sparfloxacin would enhance the stability of the drug under acidic conditions.

Conflict of Interest

Authors declared that they had no conflict of interest.

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